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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,083	11/19/2001	Zvi Cabantchik	25192	5772

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EXAMINER	
VENCI, DAVID J	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 12/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/868,083	CABANTCHIK ET AL.	
	Examiner	Art Unit	
	David J. Venci	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *September 6, 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8 and 11-22* is/are pending in the application.

4a) Of the above claim(s) *11-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-5,8 and 11-22* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *June 14, 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges Applicants' reply, filed September 6, 2006, including Applicants' amendment to claim 22 replacing "calcitonin" with "calcein".

Currently, claims 1-5, 8 and 20-22 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

The disclosure is objected to because of the following informalities:

On p. 16, lines 10-12, the sentence beginning "A second serum sample[...]" is indefinite. The purpose of this "second serum sample" in Applicants' overall method is not clear.

On p. 16, line 14, the recitation "20 ? M ferrous ammonium sulfate" is indefinite.

On p. 16, line 18, the phrase "each serum sample dilution prepared in Step 2" is indefinite. The identity of "each serum sample" in Step 2 is not clear. Whether "each serum sample" references the "sample" described on p. 16, lines 8-10 AND/OR/XOR the "second serum sample" described on p. 16, lines 10-12 is not clear.

On p. 17, lines 12-15, the sentence beginning "For generating the calibration curve[...]" is indefinite in view of the sentence on p. 16, lines 12-15 beginning "Iron standards for calibration[...]".

Whether "standard solutions" and "iron standards" contain $MnCl_2$ is not clear.

The final pH of "standard solutions" and "iron standards" is not clear.

On p. 17, lines 16-17, the phrase "the assay was carried out as described" is indefinite. The identity of the exact location in Applicants' specification referenced by "as described" is not clear.

On p. 19, line 9 and p. 20, lines 5, 8, 14 and 21, reference to "Table 1" and "Table 2" is indefinite. Examiner is unable to locate either "Table 1" or "Table 2" in Applicants' specification.

On p. 19, line 10, the phrase "the NTBI test" is indefinite. The identity of the exact location in Applicants' specification referenced by "the NTBI test" is not clear.

On p. 21, line 14, the phrase "The NTBI test" is indefinite. The identity of the exact location in Applicants' specification referenced by "The NTBI test" is not clear.

Appropriate correction is required.

Drawings

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

The drawings are objected to under 37 CFR 1.83(a):

Fig. 1 fails to show "four separate tests" (*i.e.*, Examiner is unable to distinguish four different data points) as described in the specification on page 17, line 19. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d).

The drawings are further object to because:

In Fig. 1, the physical/mathematical derivation of the sigmoidal-shaped curve is not clear.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-5, 8 and 20-22 are rejected under 35 U.S.C. 101 because the disclosed invention is inoperative and therefore lacks utility.

Notwithstanding claim indefiniteness[1] and some minor objections to the Specification, Claim 1 essentially recites a method of indirectly measuring iron by measuring a "marker" added to a "coated" surface. In claim 22, Applicants specifically identify the surface "coated" with DFO (see claim 22, step a) and the "marker" as calcein-iron (see claim 22, step b).

According to Applicants' specification, Applicants appear to measure iron by adding calcein-iron to ***EDTA-washed***, DFO-coated plates (see Specification, p. 16, "Step 3", "The plate is then washed two times in deionized water, once in 5 mM EDTA pH 8.0[...]").[2] Applicants disclose using "5 mM EDTA pH 8.0".

However, other than disclosing the use of "5 mM EDTA pH 8.0", Applicants' specification does not describe the exact procedural details for washing DFO-coated plates with EDTA, *e.g.*, volume of washing solution, washing solvent, washing duration, washing temperature, type of washing machine, etc.[3]

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[1] See *infra*, *Claim Rejections - 35 USC § 112 – second paragraph.*

[2] Examiner observes that Applicants' invention, as claimed, currently does not require any step involving an EDTA-washed plate. What little information Applicants' specification provides appears to bear no relationship to the claims under examination.

[3] According to Heller *et al.*, 22 J. APP. POLYM. SCI. 1991 (1978), the rate of washing is affected by such factors as: (1) solubility of the contents of the plate in the solvent, (2) total surface area of the plate, (3) rate of diffusion from the plate, etc.

More importantly, not only does Applicants' invention (*i.e.*, claims 1 and 22) fail to disclose a washing step, but Applicants appear to eliminate any remaining utility of their invention by adding a "biological fluid" and various other chelators and metal ions to the plate (*i.e.*, step a of claims 1 and 22) before measuring calcein-iron.[4,5,6,7]

Consequently, Applicants' invention, as claimed, will not perform its intended function of "determining the concentration" of any metal (*e.g.*, iron) and is inoperative.

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[4] See Baker, 158 METHODS ENZYMOL. 33 (1988). According to Baker, more than one NTA molecule binds to a single metal ion thereby creating multi-order equilibria (see p. 36, "Calculation of Free Metal Ion Concentration"). Applicants' invention requiring a multi-component solution of NTA, manganese, DFO and iron does not appear to take this factor into consideration.

[5] See Eftink, 278 METHODS ENZYMOL. 221 (1997). According to Eftink, in complex biological fluids, multiple binding species should be considered (see p. 225, first full paragraph, fifth sentence). Also, Applicants must determine whether the fluorescence is the same for each binding species, as well as determine whether the binding species have similar experimentally derived K_d values, or whether the binding species interact with each other (see sentence bridging pp. 237-239). Applicants' invention requiring a fluorescence measurement in the presence of a "biological fluid" having multiple binding proteins (*e.g.*, albumin, transferrin, etc.), each having multiple binding species does not appear to take these factors into consideration.

[6] See Lohman & Bujalowski, 208 METHODS ENZYMOL. 258 (1991). According to Lohman & Bujalowski, in systems having multiple binding species, the relationship between changes in binding species and changes in signal (*e.g.*, fluorescence signal) is not linear (see paragraph bridging pp. 260-261, fifth sentence). The extent of any deviation from linear behavior is usually unknown *a priori* hence the degree of error introduced into the resulting calculated K_d values is also unknown (see paragraph bridging pp. 260-261, seventh sentence).

[7] See Pain, *Current Protocols in Protein Science*, Unit 7.7 (2004). According to Pain, solutions having a third component that absorbs in the fluorescence wavelength range will have a marked effect on measurement error (see p. 7.7.7, step 10). Applicants' invention requiring a multi-component solution of NTA, manganese, DFO, iron, and various serum components does not appear to take this factor into consideration.

Claim Rejections - 35 USC § 112 – first paragraph

Claims 1-5, 8 and 20-22 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 1-5, 8 and 20-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the amendment filed November 25, 2005, appears to introduce new matter into the disclosure. The added material that is not supported by the original disclosure is as follows:

In claim 1:

A "marker released from said metal ion"

Applicants are required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112 – second paragraph

Claims 1-5, 8 and 20-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1:

In step (a), the prepositional phrases "with a surface coated" and "with a polymer-conjugated form of an iron chelator" are indefinite. The identity of the object(s) of said prepositional phrases is not clear. Whether step (a) requires adding "a surface coated" and/or "a polymer-conjugated iron chelator" to a sample is not clear. The identity of objects subject to "contacting" is not clear.

In step (a), the object "polymer-conjugated form of an iron chelator" is indefinite. Whether said object comprises iron is not clear.

In step (a), the overall purpose of "contacting the sample[...] such that said iron chelator chelates the non-bound iron in the sample of biological fluid" (paraphrasing mine) is indefinite in view of step (b), wherein "said iron chelator[...] chelates said metal ion of said complex" (paraphrasing mine). The purpose of causing a chelator to chelate iron in step (a), only to subsequently cause said chelator to release iron in step (b) is not clear. One or more essential step(s) providing a purpose for the infinitive "to thereby release" in step (b) appears omitted. See MPEP § 2172.01.

In step (b), the prepositional phrases "with a complex comprising a maker bound" and "to a metal ion" are indefinite. The identity of the object(s) of said prepositional phrases is not clear. Whether step (b) requires adding "a complex comprising a maker bound" and/or "a metal ion" to the sample and/or surface is not clear. The identity of objects subject to "contacting" is not clear.

In step (b), the phrases "said surface with a complex" lacks antecedent basis.

In step (b), the recitation of the infinitive "to thereby release" is indefinite. Whether the act or process of "releasing" is completed or performed, or merely intended, is not clear. The identity of object(s) and/or step(s), if any, required for performing "releasing" is not clear.

In step (b), the overall purpose of causing "said marker [to release] from said metal ion" (paraphrasing mine) is indefinite in view of step (a) "contacting the sample[...] such that said iron chelator chelates the non-bound iron in the sample of biological fluid" (paraphrasing mine). The purpose of simultaneously causing formation of iron—marker (*i.e.*, step b) and iron—polymer-conjugated iron chelator complexes (*i.e.*, step a) is not clear. Whether formation of iron—marker complexes in step b) confounds "determining an amount of said marker released from said metal ion" in step (c) is not clear. Whether formation of iron—marker complexes in step b) confounds "determining the concentration of the non-bound iron" in step (c) is not clear.

In step (c), the phrase "said marker released" lacks antecedent basis.

In step (c), the term "thereby" is indefinite. The identity of object(s) and/or step(s) referenced by "thereby" is not clear. Whether the object(s) and/or steps required for performing "determining an amount of said marker" are coextensive with the object(s) and/or steps required for performing "determining the concentration of the non-bound iron" is not clear.

In claim 22, step a), one or more essential step(s) for providing and/or creating "non-bound iron" appears omitted. See MPEP § 2172.01. According to Applicants' Specification, "[t]he use of nitrilotriacetate is necessary for solubilizing the NTBI" (see Specification p. 17, lines 20-21) (emphasis mine). Clarification is required.

Response to Arguments

Claim Rejections - 35 USC § 112 – first paragraph

In prior Office Action, claims 1-5, 8 and 20-21 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Specifically, the amendment filed November 25, 2005, appears to introduce new matter into the disclosure. The added material that is not supported by the original disclosure is as follows:

In claim 1:

A "marker released from said metal ion"

In response, Applicants allege support in the Specification at p. 6, step (d) (*i.e.*, Specification p. 6, lines 13-14).

Applicants' alleged support in the Specification is not sufficient to overcome this rejection. Examiner observes that the cited portion describes a "marker that has been released". The cited portion does not identify what objects the "marker" is released from, much less identify a marker released from a "metal ion". Applicants are required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112 – second paragraph

In prior Office Action, claim 1 was rejected under 35 U.S.C. 112, second paragraph, for various reasons.

In response, Applicants appear to provide argumentation premised on the position that "step (b) quantifies the unbound sites of this chelator" (see Applicants' reply, p. 7, lines 14-15) (emphasis in original).

Applicants' argument is not persuasive. Examiner is unable to locate any language in step (b) even remotely approximating Applicants' position that "step (b) quantifies the unbound sites of this chelator". Furthermore, Examiner posits that persons of ordinary skill may not be so imaginative as to import the clarifying details of Applicants' reply to arrive at whatever Applicants regard as their invention in Applicants' reply.

Claim Rejections - 35 USC § 103

In prior Office Action, claims 1-2, 5 and 20-21 were rejected under 35 U.S.C. 103(a) as being unpatentable over Tabacco *et al.* (US 4,703,015) in view of Charlton (US 4,734,375). Claim 3 was rejected under 35 U.S.C. 103(a) as being unpatentable over Tabacco *et al.* (US 4,703,015) and Charlton (US 4,734,375), as applied to claims 1 and 2, and further in view of Yegorov *et al.*, 15 FREE RADIC. BIOL. MED. 565 (1993). Claim 4 was rejected under 35 U.S.C. 103(a) as being unpatentable over Tabacco *et al.* (US 4,703,015) and Charlton (US 4,734,375), as applied to claim 1, and further in view of Guire & Chudzik (US 4,826,759). Finally, claim 8 was rejected under 35 U.S.C. 103(a) as being unpatentable over Tabacco *et al.* (US 4,703,015) and Charlton (US 4,734,375), as applied to claims 1 and 5, and further in view of Breuer *et al.*, 268 AM. J. PHYSIOL. C1354 (1995).

Notwithstanding the degree of persuasiveness, or lack thereof, of Applicants' claim amendments and argumentation, these rejections are withdrawn.

Conclusion

No claims are allowable at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Venci whose telephone number is 571-272-2879. The examiner can normally be reached on 08:00 - 16:30 (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

David J Venci
Examiner
Art Unit 1641

djv

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